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Genetics of Retinitis Pigmentosa and Other Hereditary Retinal Disorders in Western Switzerland

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Inherited retinal disorder · Switzerland · Molecular characterization · Genetic landscape · Retinitis pigmentosa · Rod-cone dystrophy · Macular dystrophy · Cone-rod dystrophy · Choroidal dystrophy · Next-generation sequencing · Pediatric retinal dystrophy

Abstract

Introduction: Mutational screening of inherited retinal disorders is prerequisite for gene targeted therapy. Our aim was to report and analyze the proportions of mutations in inherited retinal disease (IRD)-causing genes from a single center in Switzerland in order to describe the distribution of IRDs in Western Switzerland. ***Methods:*** We conducted a retrospective study of patient records. Criteria for inclusion were residence in Western Switzerland for patients and relatives presenting a clinical diagnosis of IRDs and an established molecular diagnosis managed by the genetics service of the Jules-Gonin Eye Hospital (JGEH) of Lausanne between January 2002 and December 2022. We initially investigated the IRD phenotypes in all patients (full cohort) with a clinical diagnosis, then calculated the distribution of IRD gene mutations in the entire cohort (genetically determined cohort). We analyzed a sub-group that comprised pediatric patients (≤18 years of age). In addition, we calculated the distribution of gene mutations within the most represented IRDs. Comprehensive gene screening was performed using a combined approach of different generation of DNA microarray analysis, direct sequencing, and Sanger sequencing. ***Results:*** The full cohort comprised 899 individuals from 690 families with a clinical diagnosis of IRDs. We identified 400 individuals from 285 families with an elucidated molecular diagnosis (variants in 84 genes) in the genetically determined cohort. The pediatric cohort included 89 individuals from 65 families with an elucidated molecular diagnosis. The molecular diagnosis rate for the genetically determined cohort was 58.2% (family ratio) and the 5 most frequently implicated genes per family were *ABCA4* (11.6%), *USH2A* (7.4%), *EYS* (6.7%), *PRPH2* (6.3%), and *BEST1* (4.6%). The pediatric cohort had a family molecular

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diagnosis rate of 64.4% and the 5 most common mutated genes per family were *RS1* (9.2%), *ABCA4* (7.7%), *CNGB3* (7.7%), *CACNA1F* (6.2%), *CEP290* (4.6%). ***Conclusions:*** This study describes the genetic mutation landscape of IRDs in Western Switzerland in order to quantify their disease burden and contribute to a better orientation of the development of future gene targeted therapies.

Introduction

Inherited retinal diseases (IRDs) are a group of more than 100 clinically and genetically heterogeneous disease entities caused by various mutations in around 300 genes [1]. Monogenic IRDs can be classified into outer retinal disease with primary or secondary choroidal involvement or inner retinal disease involving the vitreous. Clinically, IRDs can be classified on the basis of the predominantly affected type of cell [2]. The onset of symptoms can be insidious and variable, even among patients affected by the same type of IRD, and can occur from birth to adulthood with varying degrees of severity [2].

Multiple inheritance mode has been identified, commonly autosomal dominant (AD), autosomal recessive (AR), X-linked (XL), and mitochondrial [3]. A molecular analysis is indicated in all patients with clinical suspicion. A known genetic cause helps in confirming the type of IRD and thus both the patient's prognosis and the risk of other family members and offspring to be affected, even given that no treatment is currently available for most of these diseases.

In recent years, many studies have been underway for potential therapies [4], including gene therapies such as voretigene neparvovec-rzyl (Luxturna®), a viral vector carrying the *RPE65* gene, which is commercially available since December 2017 after FDA approval [5]. Gene therapy involving the *CHM* gene for choroideremia, the *RPGR* gene for XL retinitis pigmentosa (RP), and *CNGB3* and *CNGA3* genes for achromatopsia has been studied in humans [6–8]. Many other promising clinical trials have emerged in this field, involving the *CEP290* gene for Leber congenital amaurosis type 10, which is the subject of a clinical trial based on intravitreal injection of antisense oligonucleotide, and exon replacement therapy of *USH2A* [9, 10].

Given the progress in gene targeted therapy, molecular diagnosis is becoming relevant to patient care and the knowledge of the distribution of gene variants in a population is of increasing scientific interest. We therefore decided to conduct this retrospective study with the aim of describing the distribution of gene mutations in IRDs in Western Switzerland, based on data from a single center, the genetics service of the Jules-Gonin Eye Hospital (JGEH).

Materials and Methods

Participants

The study comprised patients residing in Western Switzerland, of all ages and with a molecular diagnosis of IRD registered in the database of the genetics service of the JGEH between January 2002 and December 2022. In order to study differences in the distribution of gene variants according to age, we divided the participants into 2 genetically determined cohorts, consisting first of all age-groups with a molecular diagnosis of IRD and second only the pediatric cohort, which included those ≤18 years of age at the time of molecular diagnosis.

Database of the JGEH Genetics Service

Every patient with a clinical suspicion of IRD is referred to, and comprehensively examined by, ophthalmologists from the ocular genetics service. Whenever possible, other family members are investigated to create the pedigree of the family unit, which is then recorded with other clinical data using a unique anonymized identification code.

The database includes digitalized clinical data extrapolated from clinical practice, in some cases from paper sources according to the year in which the patient was referred. Subject to the data available, the most relevant included clinical diagnosis, molecular diagnosis, reports of all investigations performed including slit-lamp biomicroscopy, visual acuity, and functional and imaging instrumental examinations as required.

Patient Care

As one of the country's reference ophthalmology centers, the JGEH receives patients from, physicians from all over Switzerland for a specialist examination in the field of inherited eye diseases. The recruitment area is mainly represented by Western Switzerland and its French-speaking cantons, with a small number from other German- or Italian-speaking cantons (by order of number of patients per canton: Vaud, Valais, Neuchatel, Freiburg, Valais, Jura, Ticino, Basel-Landschaft, Basel-Stadt, Zurich, Lucerne, Solothurn, and Aargau).

In the case of suspected IRD, the patient is referred to specialist ophthalmologists at the JGEH genetics service and, after a comprehensive past and family medical history (in order to build a pedigree), undergoes a full functional and anatomical investigation. Both uncorrected and best-corrected visual acuities are assessed, slit-lamp biomicroscopy performed, and intraocular pressure measured. According to the data collected and suspected diagnosis, the investigations will include color fundus photographs, short-wavelength fundus autofluorescence, spectral-domain optical coherence tomography, and functional

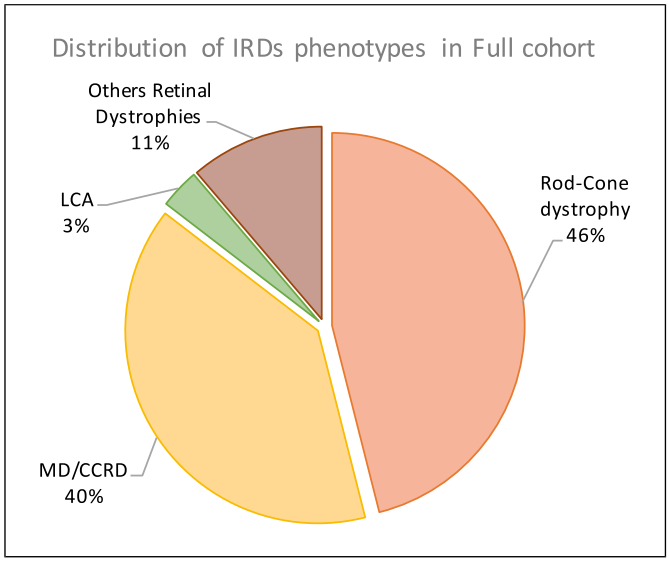

Fig. 1. Pie chart showing the distribution of IRD phenotypes in the full cohort (899 individuals); only the most frequent phenotypes are shown. The category "other retinal dystrophies" included all less represented phenotypes (Bietti crystalline retinopathy, fundus albipunctatus, late-onset retinal degeneration [L-ORD], unspecified flecked retinopathy, undefined retinal dystrophies, albinism, vitreoretinal disorders, chorioretinal dystrophies, and choroideremia).

examinations such as visual field testing, electroretinography, and electrooculography. If the suspicion of IRD is confirmed, a molecular analysis is discussed and, in certain cases, proposed to the patient and to any family members who have been investigated.

Genome Analysis

This is a retrospective study covering a time frame of about 20 years in which human genome sequencing technologies have evolved rapidly. The patients included were analyzed with different techniques depending on the period in which they were referred to the genetics service. It is necessary to mention that, in the first 5–10 years, genomic analyses were mainly represented by Sanger sequencing of single genes or small panels. A further factor is that the percentage of patients undergoing analysis was much lower in the early years due to the fact that the financial costs have only been covered by the Swiss health insurance on an automatic basis since the last 5 years.

As technologies became more sophisticated, techniques such as next-generation sequencing, whole exome sequencing, and whole genome sequencing provided more reliable and accurate results and were able to sequence a larger number of genes. This resulted in an increase in the number of cases analyzed and, for those elucidated, allowed us to better characterize the gene variants causing IRDs in the Swiss population.

We only considered gene mutations that are included in the Retinal Information Network online sources (https://web.sph.uth.edu/RetNet/sym-dis.htm) and, when not in the database, only included mutations mentioned in the literature. To establish the mode of inheritance, we referred to information from the Retinal Information Network online sources (https://web.sph.uth.edu/RetNet/sym-dis.htm) and, when the gene had multiple inheritance modes, considered the clinical inheritance pattern based on family medical history. Patients' genomic DNA was mainly extracted from peripheral blood or saliva samples but in rare cases was extracted from hair follicles or hair shafts.

Results

Full Cohort (All Patients)

The full cohort included all patients resident in Western Switzerland seen at the JGEH ocular genetics service with a clinical diagnosis of IRDs, collected from January 2002 to December 2022. We identified 899 individuals from 690 families affected by IRDs with a clinical diagnosis. The most frequently diagnosed IRD per individual was rod-cone dystrophy (RCD: 46.1%) followed by macular and cone/cone-rod dystrophies (MD/CCRD: 39.4%), Leber congenital amaurosis (3.3%), and other retinal dystrophies (11.2%), the latter consisting of a variety of less represented IRDs. These are illustrated along with the other less frequent IRDs in Figure 1.

Genetically Determined Cohort

The genetically determined cohort included participants of all ages. A total of 629 individuals from 490 families underwent molecular analysis. Of these, 285 families (400 individuals) had an elucidated molecular diagnosis, giving a 58.2% yield success. To summarize, we found pathogenic variants in 84 different genes.

The top 10 most frequent mutated genes for individuals were as follows: *ABCA4* (8.8%), *PRPH2* (6.8%), *EYS* (6.3%), *NR2E3* (5.8%), *USH2A* (5.3%), *BEST1* (4.5%), *PROM1* (4.3%), *RHO* (3.0%), *RPGR* (3.0%), and *RP2* (3.0%) (shown in Fig. 2). The top 10 most common mutated genes per family unit were as follows: *ABCA4* (11.6%), *USH2A* (7.4%), *EYS* (6.7%), *PRPH2* (6.3%), *BEST1* (4.6%), *NR2E3* (2.8%), *CHM/REP1* (2.5%), *EFEMP1* (2.5%), *RS1* (2.5%), and *CNGB3* (2.5%). These are represented together with the less frequent ones in Figure 3. Among the 20 most frequently implicated genes, there are some that are potentially transmitted in different inheritance patterns, such as *VMD2/BEST1* (16 AD and 2 AR), *NR2E3* (19 AD and 4 AR), *RHO* (11 AD and 1 AR), *PROM1* (14 AD and 3 AR), *RP1* (4 AD).

All individuals with an *ABCA4* mutation had a clinical diagnosis of MD/CCRD: Stargardt disease (31

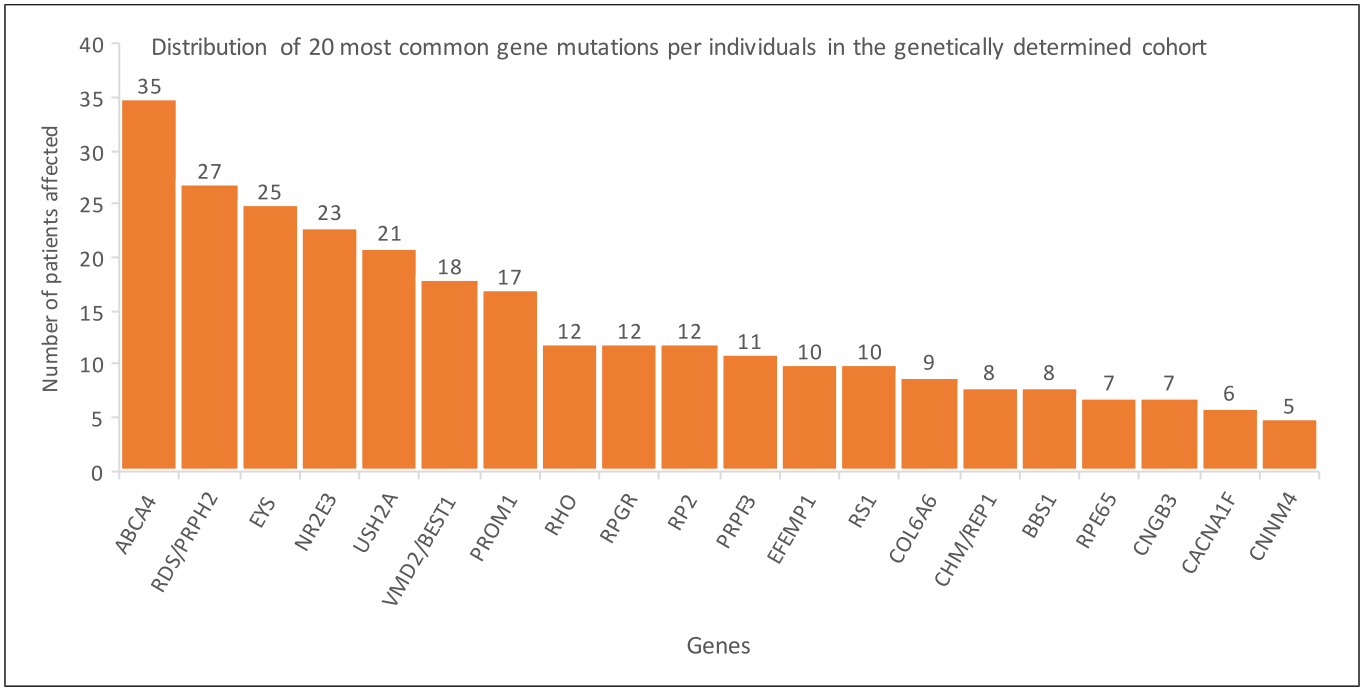

Fig. 2. Bar graph showing the 20 most involved genes in the genetically determined cohort (400 individuals) ranked by affected individuals.

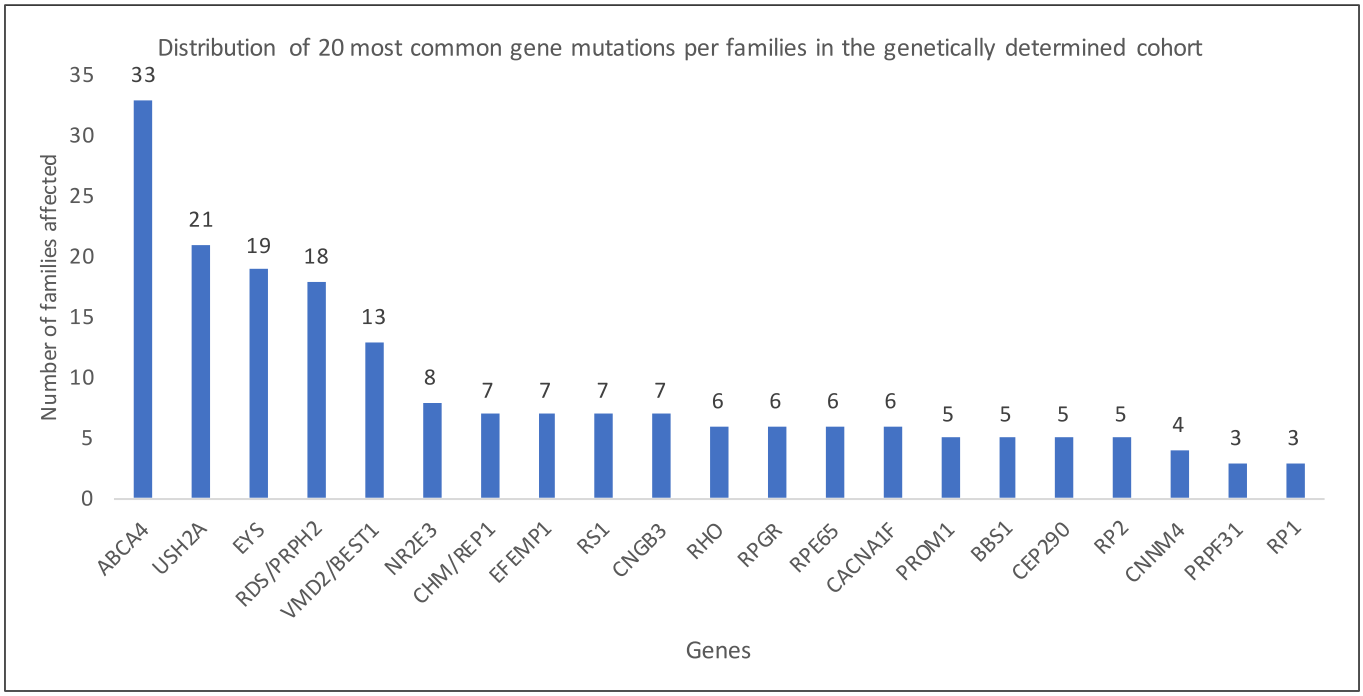

Fig. 3. Bar graph showing the 20 most involved genes in the genetically determined cohort (285 families) ranked by affected families.

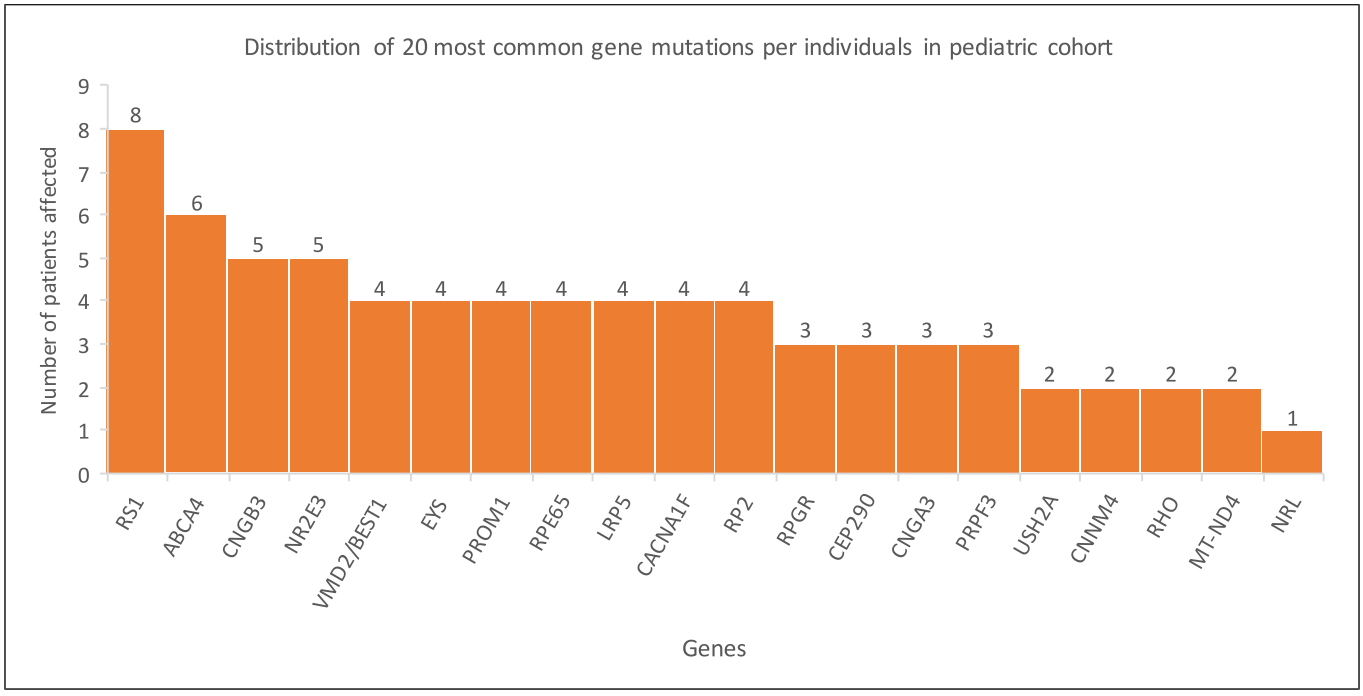

Fig. 4. Bar graph showing the 20 most involved genes in pediatric cohort (89 individuals) ranked by affected individuals.

individuals), MD (3 individuals), and CRD (1 individual). The most common mode of disease transmission in individuals was AR inheritance (48%) followed by AD inheritance (38.3%), XL inheritance (12.3%), and mitochondrial inheritance (1.3%).

Pediatric Cohort

The pediatric cohort included patients who were 18 years of age or younger at the time of molecular diagnosis. We identified 89 individuals from 65 families out of 127 tested individuals from 101 families, obtaining an elucidated family ratio of 64.35%. To summarize, we found pathogenic variants in 36 different genes.

The distribution of mutated genes for individuals was as follows: *RS1* (9.0%), *ABCA4* (6.7%), *CNGB3* (5.6%), *NR2E3* (5.6%), *CACNA1F* (4.5%), *RPE65* (4.5%), *LRP5* (4.5%), *BEST1* (4.5%), *PROM1* (4.5%), and *EYS* (4.5%) as shown in Figure 4. The distribution of gene mutations per family unit was as follows: *RS1* (9.2%), *ABCA4* (7.7%), *CNGB3* (7.7%), *CACNA1F* (6.2%), *CEP290* (4.6%), *RPE65* (4.6%), *LRP5* (4.6%), *CNGA3* (4.6%), *USH2A* (3.1%), and *RPGR* (3.1%). These are shown in Figure 5.

The following are the genes that can be transmitted in different inheritance patterns: *LRP5* (2 AD and 2 AR), *VMD2/BEST1* (4 AD), *PROM1* (4 AD), *NRL* (1 AD), *PCDH15* (1 AR). The most common mode of transmission in individuals was AR inheritance (51.7%) followed by AD inheritance (23.6%), XL inheritance (22.5%), and mitochondrial inheritance (2.3%).

RP Cohort

RP (syndromic and non-syndromic) was the most represented clinical phenotype of IRD (414 individuals), with an elucidated (118) to analyzed families (209) ratio of 56.5%. Patients suffering from autosomal dominant RP (adRP) was the most common with 41.3% of individuals (81 patients, 28 families), followed by autosomal recessive RP (arRP), which accounted for 32.1% of individuals (63 patients, 56 families), although the number of index patients for arRP was lower than in adRP given the greater number of affected patients in AD families. The RP associated with syndromic conditions represented 14.3% of individuals (28 patients, 11 families) and finally the X-linked RP (XLRP) accounted for 12.2% of individuals (24 patients, 23 families).

NR2E3 (23.5%) and *PROM1* (17.3%) were the most mutated genes in adRP. *EYS* (39.7%) and *USH2A* (20.6%) were the most prevalent mutated genes in arRP. In XLRP, RPGR (50.0%) and RP2 (50.0%) were

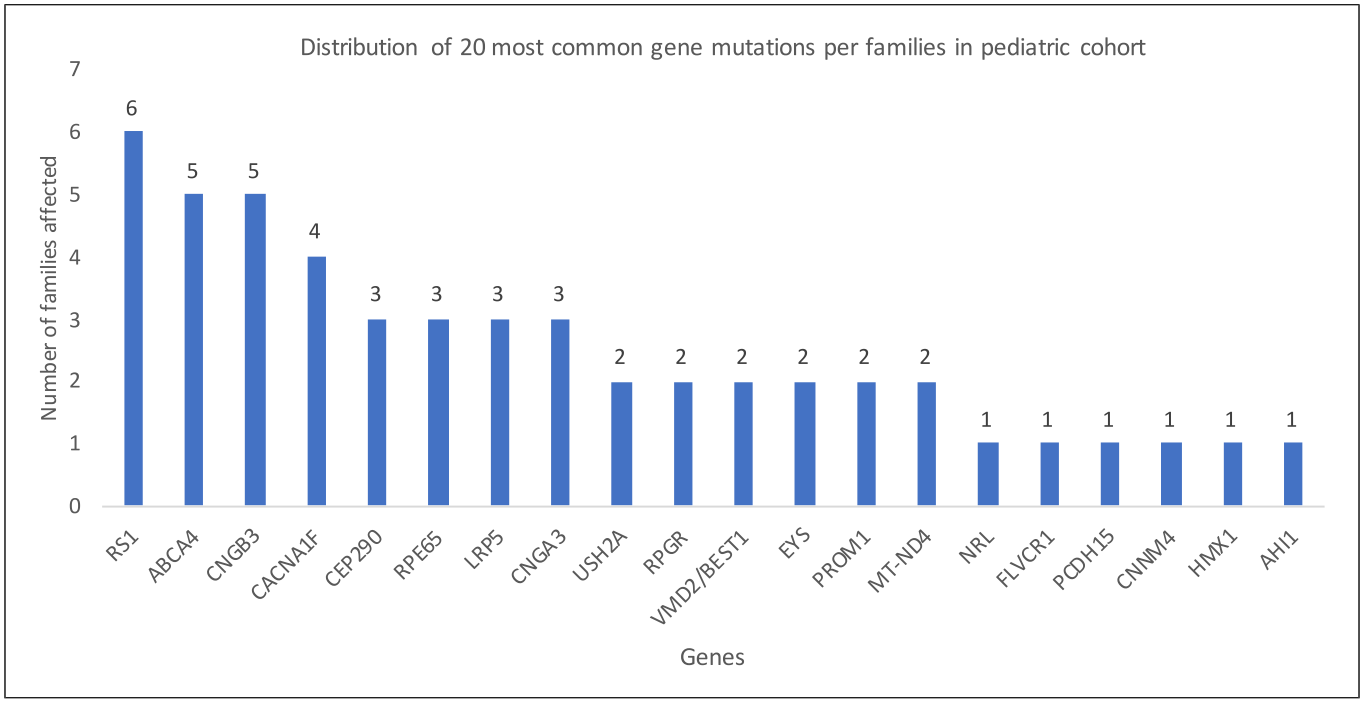

Fig. 5. Bar graph showing the 20 most involved genes in pediatric cohort (65 families) ranked by affected families.

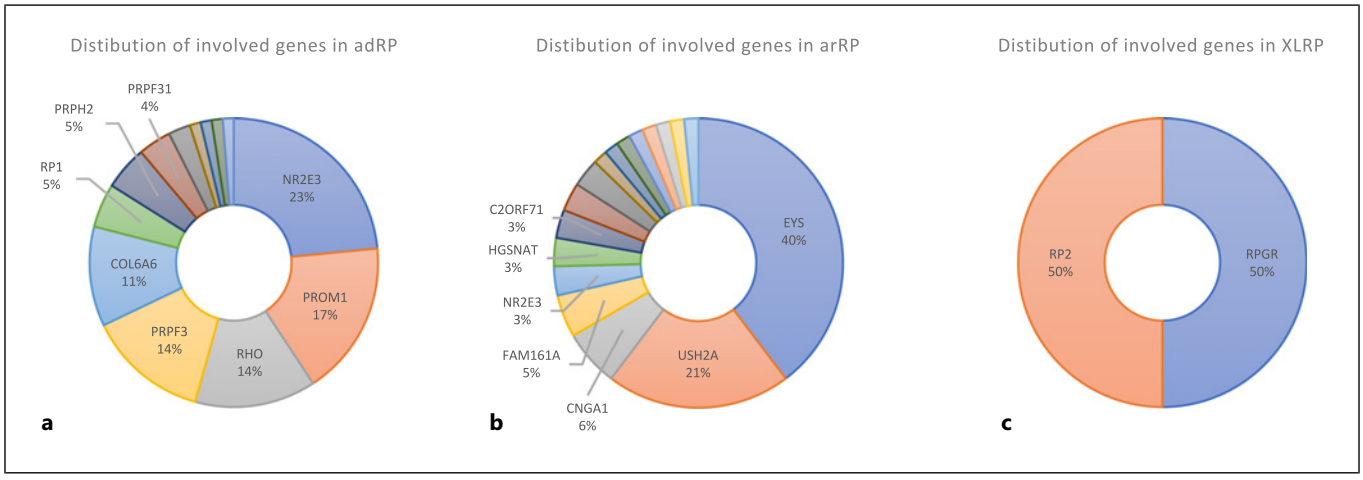

Fig. 6. Pie charts showing the distribution of most involved genes in retinitis pigmentosa (RP) cohort; only the most common mutated genes are shown. **a** Pie chart showing the distribution of mutated genes in adRP (81 individuals) ranked by individuals. **b** Pie chart showing the distribution of mutated genes in arRP (63 individuals) ranked by individuals. **c** Pie chart showing the distribution of mutated genes in XLRP (24 individuals) ranked by individuals.

found in equal numbers. Finally, *BBS1* and *USH2A* (28.6%) were the 2 most prevalent mutated genes in syndromic RPs. The distribution of gene mutations per individual and the modes of inheritance are illustrated in Figures 6 and 7.

Discussion

This is the first comprehensive study of molecular diagnosis in patients suffering from IRDs coming from a single center in Switzerland. The cohort consists of residents

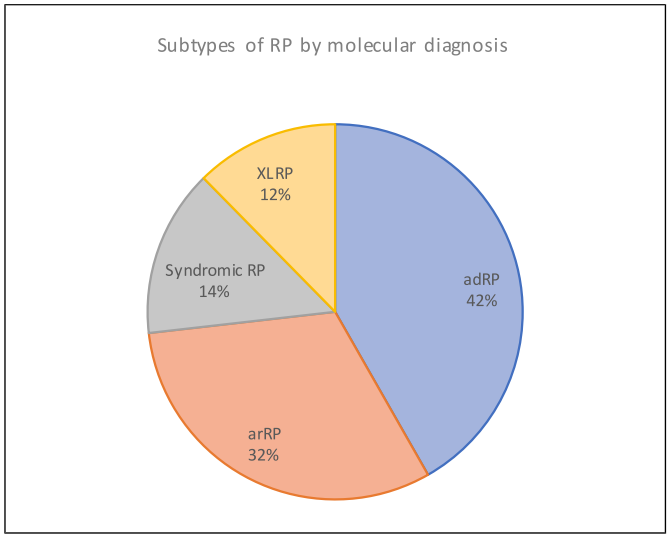

Fig. 7. Pie chart showing the distribution of retinitis pigmentosa (RP) subtype based on molecular diagnosis in RP cohort (196 individuals).

mostly living in the French and Italian parts of the country but does also include a small number of Swiss German and Swiss Italian patients living in adjacent regions. This is the largest study to date covering a period of 20 years and allowed us to create a panorama of the most prevalent IRDs in Western Switzerland during a period of significant technological evolution in the field of gene diagnosis. Furthermore, it is one of the few studies analyzing a pediatric cohort. In order to discuss our results, we reviewed the literature for comparable studies, which are shown in Table 1.

Full Cohort

We investigated the proportions of clinical phenotypes found in a cohort of 899 individuals belonging to 690 families. As shown in Figure 1, the most frequently diagnosed IRD in individuals was RCD (46.1%) followed by MD/CCRD (39.4%) and Leber congenital amaurosis (3.3%). These results are similar to several large studies, such as that carried out in England concerning more than 1,000 individuals where RCD, MD, and CRD were the three most commonly found phenotypes [9]. Other large studies conducted in Germany [10] and Ireland [27] are also aligned with our results.

Genetically Determined Cohort

The family molecular diagnosis rate was 58.2%. This rate is comparable to other large studies carried out in Spain [13], the USA [24], Israel [18], and Denmark [28] in which the ratio varies between 48% and 76%. It is important to take into account that our study is spread over a period of around 20 years. In the early years, all exome analysis was proposed to only a small percentage of patients due to less accurate genomic sequencing technologies and a smaller panel of genes than today. Our ratio is thus likely to be underestimated compared to the current effectiveness of genomic analysis.

ABCA4 (11.6% of families and 8.8% of individuals) was the most common mutated gene for both families and individuals and *USH2A* (7.4% of families) was the second most common among families. We can affirm that this result is shared by most of the large studies that have been conducted in different parts of the world such as England [9], Germany [10], Brazil [23], Korea [15], and Israel [18]. In our study, we found that all individuals with an *ABCA4* mutation had a clinical diagnosis of MD/CCRD, which included 31 cases of Stargardt disease, 3 cases of macular dystrophy, and 1 case of CRD. The top 5 most prevalent genes per family (*ABCA4, USH2A, EYS, PRPH2, BEST1*) also included *PRPH2* and *BEST1*, which also appear in a large study carried out at Moorfields Eye Hospital in England [9].

It is estimated that *EYS* represents one of the most frequently encountered genes in Asian cohorts such as in Korea [15], in an RP cohort in Japan [29], and in a cohort of non-syndromic IRDs in China [17]. It is also remarkable that in a recent Portuguese study *EYS* represents the most prevalent gene and is considered to be the source of a founder mutation [11]. In the current study, *EYS* (6.7% of families) is the third most prevalent gene in families, which is uncommon compared to other European studies where it is not often found among the top 5 most prevalent genes. Switzerland is one of the European countries with the highest percentage of permanent resident foreigners and, among the latter, Portuguese nationality is the third most commonly found almost on equal terms with Italians and Germans [30].

Mitochondrial transmission genes were not very common (1.3%). It is probable that our cohort underestimates this type of transmission due to a greater difficulty in molecular diagnosis.

Pediatric Cohort

By investigating a pediatric cohort, we attempted to identify any differences compared to the determined genetical cohort, in order to have a better understanding of it. Currently, there are not many studies of this type involving pediatric cohorts.

We obtained a family molecular diagnosis rate of 64.4%. Compared to the determined genetical cohort, molecular diagnosis is significantly more successful (64.4% vs. 58.2%). This may be due to a higher specificity of the clinical features of pediatric IRDs and a more frequent positive family history.

Table 1. Findings of selected studies which are comparable to the current study classified by year of publication

Year of publication	Study country	Molecularly diagnosed, *N* (genes, *n*)	Most frequently implicated genes	Authors
Current study	Switzerland	400 individuals (84 genes)	*ABCA4, PRPH2, EYS, NR2E3, USH2A*	Conti et al.
2023		285 families	*ABCA4, USH2A, EYS, PRPH2, BEST1*	
2023	Portugal	174 index individuals (57 genes)	*EYS, ABCA4, RPGR, USH2A, RHO*	Peter et al. [11] (2023)
2022	India	70 individuals	*ABCA4, CERKL, GUCY2D, AIPL1, PROM1*	Gopinath et al. [12] (2023)
2021	Spain	2,100 families (142 genes)	*ABCA4, USH2A, RS1, CRB1, RHO*	Perea-Romero et al. [13] (2021)
2021	Mexico	105 individuals (48 genes)	*ABCA4, RPGR, CRB1, USH2A, ARL6*	Villanueva-Mendoza et al. [14] (2021)
2021	Korea	86 individuals (35 genes)	*USH2A, ABCA4, EYS, RP1, MYO7A*	Ma et al. [15] (2021)
2021	Poland (non-syndromic)	115 individuals	*ABCA4, RPGR, CNGA3, RHO, CEP290*	Tracewska et al. [16] (2021)
2020	UK	3,197 families (135 genes)	*ABCA4, USH2A, RPGR, PRPH2, BEST1*	Pontikos et al. [9] (2020)
2020	China (non-syndromic)	481 individuals (73 genes)	*CYP4V2, USH2A, ABCA4, RPGR, EYS*	Liu et al. [17] (2021)
2020	Germany	1,528 individuals (112 genes)	*ABCA4, USH2A, RPGR, RHO, PRPF31*	Weisschuh et al. [10] (2020)
2019	Israel	1,369 families (129 genes)	*ABCA4, USH2A, FAM161A, CNGA3, EYS*	Sharon et al. [18] (2020)
2019	Norway	207 individuals (56 genes)	*ABCA4, USH2A, BEST1, RHO, RS1*	Holtan et al. [19] (2020)
2019	UAE (children)	71 individuals (26 genes)	*ABCA4, KCNV2, CRB1, CNGA3*	Khan [20] (2019)
2019	Finland (children)	41 families (17 genes)	*RS1, GUCY2D, RPGR*	Avela et al. [21] (2019)
2019	Iran	36 families (19 genes)	*ABCA4, RPE65, CERKL, RPGRIP1*	Tayebi et al. [22] (2019)
2018	Brazil	400 individuals (66 genes)	*ABCA4, CEP290, USH2A, CRB1, RPGR*	Motta et al. [23] (2018)
2017	USA	760 families (104 genes)	*ABCA4, USH2A, RPGR, RHO, PRPH2*	Stone et al. [24] (2017)
2017	The Netherlands	136 individuals (56 genes)	*USH2A, EYS, ABCA4, RPGR, GUCY2D*	Haer-Wigman et al. [25] (2017)
2016	Switzerland	58 individuals (18 genes)	*ABCA4, C2orf71, RP1, CEP290, FLVCR1*	Tiwari et al. [26] (2016)

The first column shows the year of publication of the study, the second column the reference country of the study. The third column shows the number of affected individuals/families with a molecular diagnosis and the number of different involved genes found in the entire cohort (when possible). The fourth column shows the 5 most frequently involved genes (it was not always possible to extract the five most prevalent genes). The fifth column shows the study's authors.

RS1 was the most frequently found gene among families (6) and individuals (8). All individuals were male and its associated clinical phenotype was X-linked juvenile retinoschisis. This finding is shared by a Finnish study that considered a cohort of 68 children [21], and *RS1* was the second most prevalent gene in a cohort of 452 children studied in England [9]. X-linked juvenile retinoschisis is estimated to affect 1:5,000 to 1:20,000 young males with a XL recessive pattern of inheritance [31, 32]. Three of the five most implicated genes are also found in the five most mutated genes in the British pediatric cohort (*ABCA4, RS1, CACNA1F*) [9].

When comparing the results to those obtained with the genetically determined cohort (77.5% of adults), we observed important differences such as the absence of genes such as *PRPH2* (as expected) and *USH2A* in the top five most common genes. This could reflect the later onset of visual symptoms compared to other clinical symptoms (e.g., hearing disabilities) and thus a later average age of diagnosis.

Another remarkable difference was the distribution of inheritance pathways. In the pediatric cohort, the proportion of AR and XL inheritance genes increased and AD inheritance genes decreased compared to the genetically determined cohort. This is probably due to the greater severity and earlier onset of symptoms of AR and XL IRDs compared to those with AD inheritance.

RP Cohort

RP being the most represented IRD, we also studied it separately. The term RP is used to describe a heterogeneous group of IRDs that have in common a retinal pigment accumulation and a loss of photoreceptors [33]. They are caused by more than 90 different genes with different transmission patterns (accessed on November 1, 2022) [34]. Its worldwide prevalence is estimated to be 1:3,500 individuals [33, 35]. In our study, the elucidated (116) to analyzed families (207) ratio was 56.5%, which is comparable to other studies conducted in Spain [13], Ireland [27], and Korea [15] where the molecular diagnosis ratio ranged between 71% and 49.8%.

The most frequent inheritance pattern was AD (adRP, 41.3%). *NR2E3* (23.5%) and *PROM1* (17.3%) were the most commonly mutated genes. This finding differs from the results of other countries where the most frequently reported gene was often *RHO*, whereas in the current study it ranks third in frequency [9, 13, 15, 27, 29]. The high incidence of *NR2E3* and *PROM*1 (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000536036) is due to large elucidated families of our cohort (10 and 15 patients, respectively) and is of note that families diagnosed with arRP (56) are relatively more numerous than adRP families (28). It is interesting to mention that many *PROM1* and *NR2E3* mutations in our cohort possess an AD character associated with an RP phenotype, a finding that is supported by a study of seven families in which AD mutations were associated with clinical phenotypes of bull's eye maculopathy, rod, rod-cone, and macular dystrophies [36]. Overall, 32.1% of genes included were characterized by AR transmission (arRP), and among them *EYS* (39.7%) and *USH2A* (20.6%) were the most frequent genes as in studies conducted in Korea, Japan, Brazil, and Germany [15, 23, 29, 37].

RPGR (50%) and *RP2* (50%) were found in equal amounts causing XLRP. RPGR is the most common mutated gene found by the majority of other studies worldwide, but RP2 also figures in a number of studies [9, 13, 15, 27, 29].

Conclusions

We have, for the first time, described the IRDs genetic landscape in Western Switzerland, achieving a better understanding of the true proportions attributable to different mutated genes. This study highlights the importance of molecular diagnosis as a useful tool for a better understanding of the disease and clinical management of the patient. Knowledge of the IRDs genetic base is becoming fundamental in the context of continuous scientific progress in gene targeted therapies and we hope that our work may contribute to their further development.

Study Limitations

It is necessary to interpret the results of our study considering the limitations characterizing retrospective cohort studies, such as possible errors concerning the clinical assessment of the patient or, in some cases, the lack of input for the data analyzed, which we have tried to correct wherever possible. Moreover, given that our study covers a long period of time during which technology has evolved, it is likely that some mutations have been overestimated, such as those in genes that were already included in the first genomic analysis panels, while other mutations have been underestimated, such as those that eluded earlier genomic analysis (mitochondrial genes or exonic mutations).

In recent years, with the advent of next-generation sequencing, the number of genes analyzed has increased and the costs of analysis decreased. This has enabled us to offer more and more patients the option of molecular diagnosis, which was not the case in the first years of our study. As already mentioned in the discussion, this has probably led to an underestimation of the molecular diagnosis ratio obtained.

The pediatric cohort has a small number of individuals, thus producing a possible sample size bias. It was not always possible to establish retrospectively the age of onset of symptoms, a criterion that could not thus be used for

inclusion in the study. We therefore used the age of molecular diagnosis, which probably resulted in an underestimated pediatric cohort. In the same manner, some pediatric patients might have had molecular diagnosis while asymptomatic, in the context of an entire molecular family analysis.

Finally, we were not able to analyze other important data such as ethnicity or nationality of origin due to the variability of data collected over the years. Switzerland being one of the countries with the highest rate of permanent resident foreigners, more detailed investigation could be of interest in any further study.

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Statement of Ethics

This retrospective study was designed in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of "Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD)" (Authorization CER-VD n° 340/15). The need for informed consent was waived by the Ethics Committee of "Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD)" (Authorization CER-VD n° 340/15). In addition, patients who underwent the molecular analysis signed informed consent stating that the data obtained could be used for scientific research purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Substantial contributions to the conception and design of the work: Hoai Viet Tran. Analysis and interpretation: Giovanni Marco Conti, Carlo Rivolta, Pascal Escher, Daniel Francis Schorderet, and Hoai Viet Tran. Data collection and review of the work: Veronika Vaclavik, Carlo Rivolta, Pascal Escher, Daniel Francis Schorderet, Francis L. Munier, and Hoai Viet Tran. Drafting of the work: Giovanni Marco Conti and Hoai Viet Tran. Final approval of the version: Giovanni Marco Conti, Veronika Vaclavik, Carlo Rivolta, Pascal Escher, Daniel Francis Schorderet, Francis L. Munier, and Hoai Viet Tran.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author [H.V.T.] upon reasonable request. Further inquiries can be directed to the corresponding author.

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